REMARKS

Claims 1 and 6-14 are currently pending. Claims 2-5 have been canceled without prejudice. No new matter has been added.

The Applicants expressly reserve the right to prosecute further the same or similar claims in subsequent patent applications claiming the benefit of priority to the instant application. 35 USC § 120 and § 121.

Claim Rejections - 35 U.S.C. § 103(a)

Claims 1 and 6-14 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Hill *et al.* ("Hill"; WO 01/85702) in view of Beck *et al.* ("Beck"), Rosen *et al.* ("Rosen") and Wade *et al.* ("Wade"). The Applicants respectfully traverse.

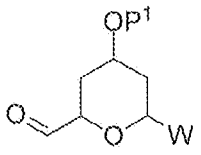
Legal Standard

To establish a *prima facie* case of obviousness, a number of criteria must be met. For example, all of the limitations of a rejected claim must be taught or suggested in the prior art references relied upon by the Examiner; or they must be among the variations that would have been "obvious to try" to one of ordinary skill in the relevant art in light of the cited references. Moreover, one of ordinary skill in the relevant art must have a reasonable expectation of success in light of the cited combination of references. Importantly, the reasonable expectation of success must be found in the prior art, and may not be based on the Applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q. 2d 1438 (Fed. Cir. 1991); *see* MPEP § 2143 - § 2143.03 for decisions pertinent to each of these criteria.

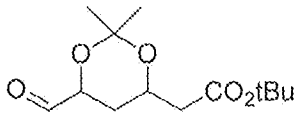
Scope and Content of the Prior Art

The rejected claims are directed to a process for the preparation of a compound of formula (7), comprising the steps of: a) hydroxylating a compound of formula (1) to give a compound of formula (2); oxidizing a compound of formula (2) to give a compound of formula (3); c) coupling a compound of formula (3) with a compound of formula (4) to give a compound of formula (5) or a compound of formula (6); and (d) and (e) subjecting the compound to ring opening and removal of any protecting groups to give a compound of formula (7).

The Examiner contends that Hill teaches the use of Wittig-type reactions for making rosuvastatin using compound (E), and asserts that this compound is "equivalent to compound (3) of the present claims". (For compound (3), P^1 represents hydrogen or a protecting group, W represents =O or $-OP^2$, and P^2 represents hydrogen or a protecting group.) However, the Applicants respectfully assert that compound (E) is not equivalent to compound (3).



Compound (3)



Compound (E)

The Wittig-type reaction described in Hill (method 4 on page 13) is conducted by deprotonating compound (D) with NaHMDS, followed by adding the resultant anionic species to compound (E). In order for the reaction to proceed with a reasonable yield and purity, the anionic species must undergo nucleophilic attach on the aldehyde selectively over other competing reactions. An example of a problematic competing reaction would be a deprotonation reaction in which the anionic species removes a hydrogen form another species.

For compound (3), P^1 or P^2 may be hydrogen. The pKa of an alcohol is about 30. (For pKa values, *see* F. G. Bordwell *Acc. Chem. Res.* **1988**, *21*, 456). This value is roughly the same as a linear ester, which have pKa values of around 30. Alternatively, in compound (3) W may be =O, resulting in the formation of a six-membered lactone. Six-membered ring lactones have pKa values of around 25. Based on the pKa values, a person of skill in the art would expect that compound (3) would be deprotonated by the phosphonate anion (compound (D)) rather than undergoing nucleophilic attack.

Moreover, for steric reasons, a person of skill in the art would expect that compound (E) would be less likely to be deprotonated than compound (3). (This is particularly true when P^1 and P^2 of compound (3) are hydrogen.) The dimethyl acetal and tert-butyl ester groups of compound (E) are bulky groups positioned on either side of the most acidic position of compound (E). The anion of compound (D) would be likewise quite bulky. Thus, a significantly smaller portion of the anionic species will deprotonate rather than make nucleophilic attack on the aldehyde of compound (E).

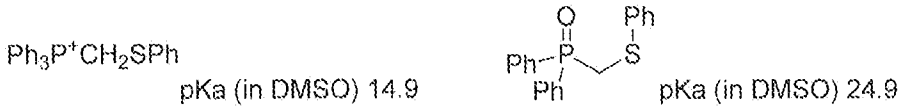
Thus, overall a person of skill in the art would not consider that compound (E) and compound (3) are equivalent compounds when considering the Witting-type reaction conditions taught in Hill.

Ascertaining the Differences Between the Prior Art and the Claims at Issue/Resolving the Level of Ordinary Skill in the Pertinent Art

The Examiner points out that Hill does not teach the synthesis of compound (3). However, the Examiner asserts that Beck provides this teaching, and thus one of skill in the art would combine Beck and Hill to arrive at the Applicants' claimed process. The Applicants respectfully disagree for the reasons set forth below.

The Examiner categorizes the alkene formation reactions in Hill and Beck as "Wittig-Horner condensations". However, the reactions in Hill and Beck are quite different, and should not be placed in the same category. The Wittig-type reaction in Hill is conducted on a phosphorus oxide, and proceeds via the formation of an anionic species. The Wittig reaction of Beck is conducted on a phosphonium salt, and proceeds via an ylide, a species with localized negative and positive charges but which has no net charge. These reactions proceed under different conditions, via different mechanisms, and often afford products with different *E/Z* ratios.

For example, the Applicants point to the differences in pKa of the compounds depicted below.



The Wittig ylide is a substantially weaker base (pKa 14.9) than the phosphorus oxide anion (pKa 24.9). Accordingly, there will be a lower amount of competitive deprotonation in a Wittig reaction than in the reaction type disclosed in Hill. Thus, a person of skill in the art would appreciate that compound (3) would be inappropriate in the reactions of Hill when compared to compound (E), which is described therein. Moreover, a person of skill in the art would not consider the Hill reaction and the Wittig reaction to be equivalent, nor would these compounds be equivalent under Horner-Wadsworth-Emmon (HWE) conditions.

Second, Beck teaches that "compound 5 can be prepared through Swern oxidation of the corresponding alcohol 13, obtained stereoselectively from glucose". *See* Beck, page 5, col. 2. The Applicants note that compound 5 of Beck is similar to compound (3) of Applicants' claimed process, and compound (3) is prepared by oxidation of an alcohol (compound (2)). However, compound (2) of Applicants' claimed process is not prepared from glucose, but is prepared by hydroxylating a halo compound, compound (2).

The Examiner asserts that Beck "provides no details" regarding the conversion of glucose to alcohol 13. To the contrary, Beck provides a citation to Yang *et al.* (Tetrahedron Lett. 23: 4305 (1982)), and this document provides details regarding methods of conversion. (See Exhibit A.) In seeking to synthesize compound 13, one of skill in the art would, having read Beck, refer to this citation. Thus, the Applicants contend that Beck does provide one of skill in the art with details of the synthesis of alcohol 13. Based on the teachings of Beck, the Applicants contend that one of skill in the art would not combine Hill with Beck, because Beck teaches away from the Applicants' claimed process in which compound (2) is prepared by hydroxylating compound (1).

The Examiner has combined Rosen with Beck with the intention of teaching the synthesis of compound (3) from compound (2). Rosen teaches the synthesis of iodide 36, and the Examiner contends that the conversion of iodides to alcohols would be within the general knowledge of one of skill in the art. Thus, the Examiner asserts that one of skill in the art would arrive at the claimed process by combining Hill, Beck and Rosen. The Applicants respectfully disagree.

One of skill in the art would not have had a reasonable expectation of success in arriving at the claimed process based on the cited combination of references. First, the person of skill in the art would understand from Beck that alcohol 13 should be made from glucose according to the method of Yang. Also, combining the teachings of Rosen would result in an inefficient and costly synthetic process. Thus, based on the cited teachings, one of skill in the art would not have arrived at the Applicants' claimed process.

Accordingly, the Applicants respectfully request the withdrawal of the claim rejections under 35 USC § 103(a).

Double Patenting

U.S. Patent Application No. 11/721,858

Claims 1 and 6-14 stand provisionally rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 1-5 of copending U.S. Patent Application No. 11/721,858 ("the '858 application") in view of Beck. Because any double patenting rejection would be based on the final form of the claims, Applicants ask the Examiner to hold the double patenting rejection in abeyance until the rejected claims are indicated as otherwise in condition for allowance.

FEES

The Applicants believe that the fees due in connection with the filing of this Response have been paid. Nevertheless, the Commissioner is hereby authorized to charge any unpaid required fees to our Deposit Account No. **06-1448**, reference **HGX-005.01**.

CONCLUSION

The Applicants believe that the pending claims are in condition for allowance. If a telephone conversation with Applicants' Agent would expedite prosecution of the above-identified application, the Examiner is urged to contact the undersigned.

Respectfully submitted,

/Sharon M. Walker/

Date: February 21, 2012

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Exhibit A

Tetrahedron Letters,Vol.23,No.42,pp 4305-4308,1982 0040-4039/82/424305-04$03.00/0
Printed in Great Britain

MEVINIC ACIDS AND ANALOGUES: PREPARATION OF A KEY CHIRAL INTERMEDIATE

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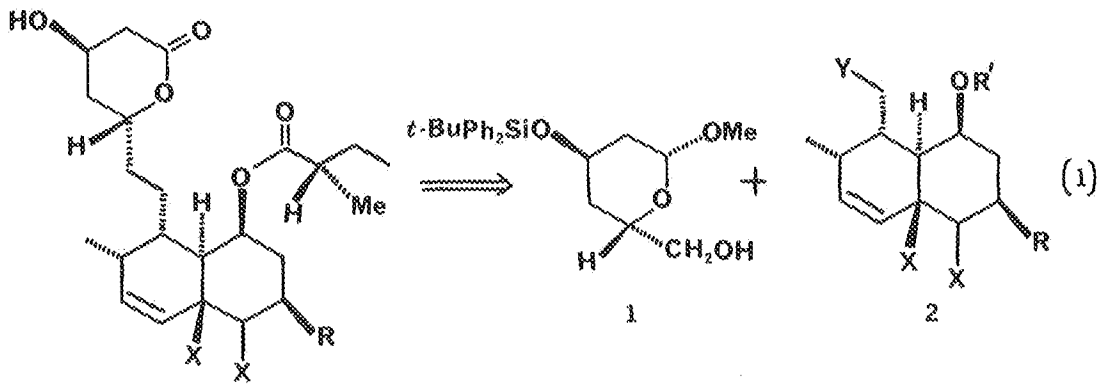
Summary: The preparation of methyl 3-O-tert-butyldiphenylsilyl-2,4-dideoxy-β-D-erythro-hexopyranoside, a key chiral intermediate for mevinic acids, and its elaboration into four mevinate analogues are described.

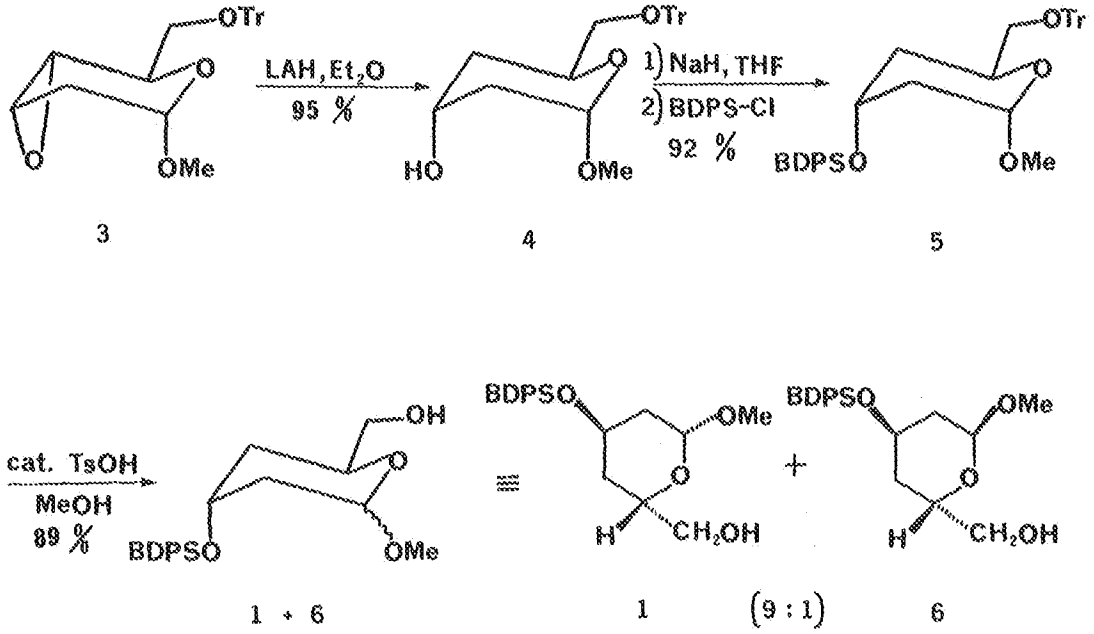
Mevinic acids[1-4] are extremely potent competitive inhibitors[5] of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in cholesterol biosynthesis. They are distinguished by a hexa or octahydronaphthalene bearing an ethylene linked β-hydroxy-δ-lactone appendage which closely resembles the HMG moiety of HMG-CoA and consequently are thought[6] to be competitive with respect to this substrate. The current synthetic interest[7] in this group of fungal metabolites is due largely to their potential in the treatment of hypercholesterolemia and established usefulness as adjuncts in biochemical research. In our antithetic analysis, we envisioned a general approach joining suitably protected lactone 1 and hydronaphthalene 2 fragments via the ethylene bridge (eq. 1). Reported herein are a brisk, high-yield synthesis of 1 with the requisite absolute stereochemistry and its elaboration into four mevinate analogues, 10a-c and 13.



Mevinolin: R=Me,X=$\Delta^{4a,5}$ Dihydromevinolin: R=Me,X=H
Compactin: R=H,X=$\Delta^{4a,5}$ Dihydrocompactin: R=X=H

The known[8] epoxy-trityl ether 3, available in 62% yield from commercially available tri-O-acetyl-D-glucal, was reduced to 3-α-hydroxypyranoside 4[9,10] by lithium aluminum hydride (LAH) in ether at room temperature for 1 h (Scheme I). Treatment of 4 with sodium hydride and t-butyldiphenylsilyl chloride (BDPS-Cl) in tetrahydrofuran (THF) at room temperature for 12 h afforded silyl ether 5. Detritylation using a catalytic amount of p-toluenesulfonic acid (TsOH) in methanol for 12 h resulted in an equilibrium mixture of anomers 1 and 6 (9:1) which could be separated chromatographically (SiO_2, ether/hexanes 1:1, $R_f \sim 0.15$ and 0.20 for 1 and 6, respectively). Although both anomers are suitable for conversion to mevinic acids, only 1 was used in subsequent work.

Scheme I

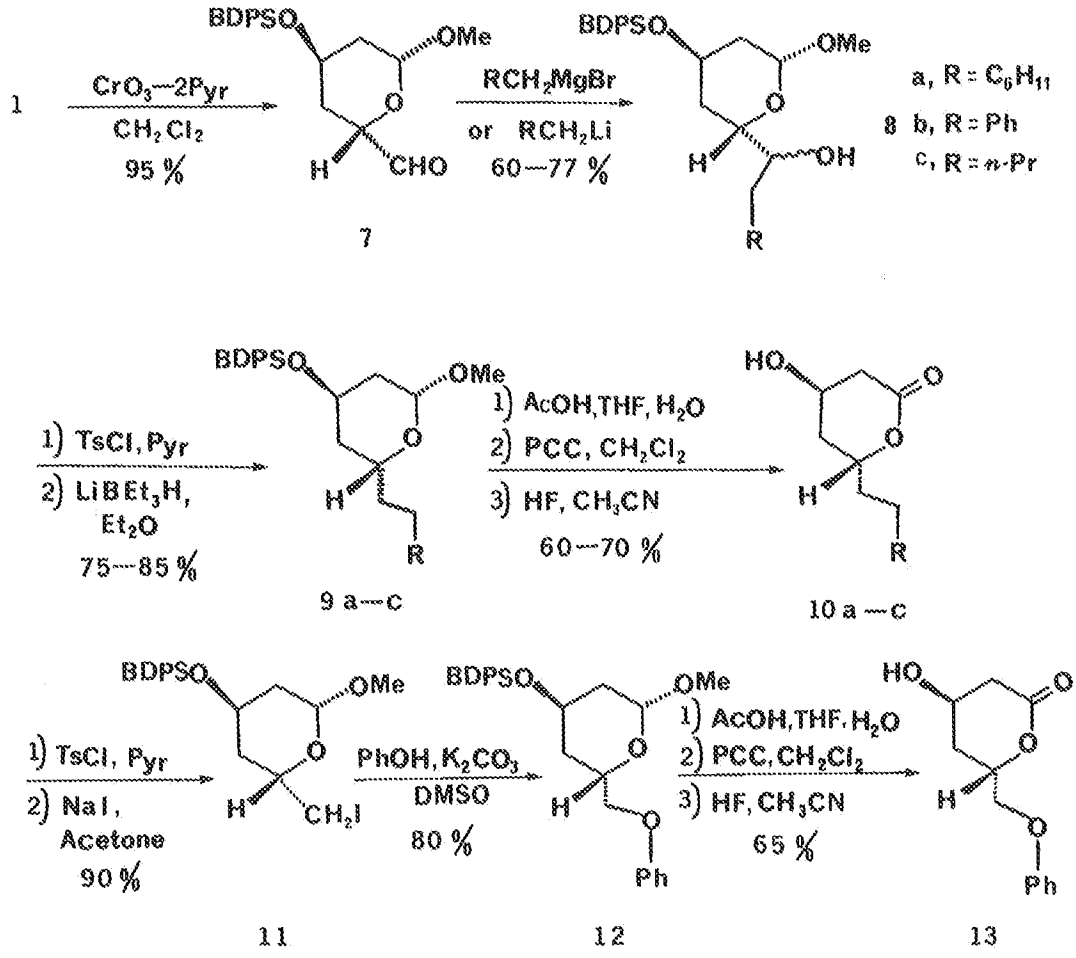


Tr = trityl; BDPS = t-butyldiphenylsilyl

Oxidation of 1 to aldehyde 7 by chromium trioxide-pyridine complex[11] proceeded smoothly in dry methylene chloride over 1 h (Scheme II). Addition of cyclohexylmethylmagnesium bromide, benzylmagnesium bromide, and n-butyllithium to 7 in ether at -20°C gave the corresponding alcohols 8a-c, respectively. Tosylation with tosyl chloride in pyridine followed by lithium triethylborohydride reduction generated 6-alkylpyranosides 9a-c. Alternatively, tosylation of 1 and displacement with sodium iodide in refluxing acetone for 24 h gave iodide 11. Treatment of 11

with excess phenol in dimethylsulfoxide (DMSO) in the presence of potassium carbonate at 52°C for 12 h yielded phenyl ether 12 as the sole product. The desired δ-lactone analogues 10a-c and 13[12] were prepared readily by sequential hydrolysis in AcOH/THF/H_2O (3:2:2) at 70°C for 5 h, pyridinium chlorochromate (PCC) oxidation in methylene chloride, and desilylation with excess 48% hydrofluoric acid in acetonitrile at 46°C for 15 h. The total synthesis of several mevinic acids using 1 and the elaboration procedures described above will be reported in due course.

Scheme II



BDPS = t-butyldiphenylsilyl

Acknowledgment: This work was supported by USPHS NIH Research Grant PO1-HL-20948 and by a grant-in-aid from the American Heart Association with funds contributed in part by the Texas affiliate.

References and Notes

1. The name mevinic acid as proposed for the parent system (see ref. 2a) refers to the free acid form but is used here to include the δ -lactone form.

2. Mevinolin: (a) A.W. Alberts, J. Chen, G. Kuron, V. Hunt, J. Huff, C. Hoffman, J. Rothrock, M. Lopez, H. Joshua, E. Harris, A. Patchett, R. Monaghan, S. Currie, E. Stapley, G. Albers-Schonberg, O. Hensens, J. Hirshfield, K. Hoogsteen, J. Liesch, and J. Springer, Proc. Natl. Acad. Sci. USA, 77, 3957-3961 (1980); (b) A. Endo, J. Antibiotics, 32, 852-854 (1979).

3. Compactin: A.G. Brown, T.C. Smale, T.J. King, R. Hasenkamp, and R.H. Thompson, J.C.S. Perkin I, 1165-1170 (1976); A. Endo, M. Kuroda, and Y. Tsujita, J. Antibiotics, 29, 1346-1348 (1976).

4. Dihydromevinic acids: G. Albers-Schonberg, H. Joshua, M.B. Lopez, O.D. Hensens, J.P. Springer, J. Chen, S. Ostrone, C.H. Hoffman, A.W. Alberts, and A.A. Patchett, J. Antibiotics, 34, 507-512 (1981); Y.K.T. Lam, V.P. Gullo, R.T. Goegelman, D. Jorn, L. Huang, C. DeRiso, R.L. Monaghan, and I. Putter, ibid., 34, 614-616 (1981).

5. Reviews: A. Endo, Trends Biochem. Sci., 6, 10-13 (1981); A. Endo, Methods Enzymology, 72, 684-689 (1981).

6. K. Tanzawa and A. Endo, Eur. J. Biochem., 98, 195-201 (1979).

7. N.-Y. Wang, C.-T. Hsu, and C.J. Sih, J. Amer. Chem. Soc., 103, 6538-6539 (1981); R.L. Funk and W.E. Zeller, J. Org. Chem., 47, 180-182 (1982); S. Danishefsky, S. Kobayashi, and J.F. Kerwin, Jr., ibid., 47, 1981-1983 (1982); J.D. Prugh and A.A. Deana, Tetrahedron Lett., 23, 281-284 (1982); E.A. Deutsch and B.B. Snider, J. Org. Chem., 47, 2682-2684 (1982).

8. E.J. Corey, L.O. Weigel, A.R. Chamberlin, and B. Lipshutz, J. Amer. Chem. Soc., 102, 1439-1441 (1980).

9. For all new compounds, satisfactory ir, nmr, and mass spectral data were obtained on chromatographically homogeneous samples.

10. Physical data for 1: mp 97-98°C; $[\alpha]_D^{24}$ -11.2° (C=4.03, $CHCl_3$); nmr ($CDCl_3$) δ 1.08 (9H,s), 1.30-2.20 (4H,m), 3.50 (3H,s), 3.40-3.70 (2H,m), 4.10 (1H,m), 4.28 (1H,m), 4.86 (1H,dd,J=2.5, 10.5 Hz), 7.36 (6H, m), 7.60 (4H, m); 4: mp 100-102°C; $[\alpha]_D^{24}$ 45.3° (C=4.30, $CHCl_3$); nmr ($CDCl_3$) δ 1.40-2.00 (4H,m), 3.12 (2H,m), 3.40 (3H,s), 3.56 (1H,d,J=10Hz), 3.90-4.40 (2H,m), 4.84 (1H,brs), 7.00-7.60 (15H,m); 5: mp 53-55°C; $[\alpha]_D^{24}$ 27.5° (C=4.18, $CHCl_3$); nmr ($CDCl_3$) δ 1.08 (9H,s), 1.20-1.80 (4H,m), 3.04 (2H,m), 3.40 (3H,s), 4.08 (1H,m), 4.44 (1H,m), 4.68 (1H,m), 7.10-7.80 (25H,m).

11. R.Ratcliffe and R. Rodehorst, J. Org. Chem., 35, 4000-4002 (1970).

12. Physical data for 10a: mp 65-67°C; nmr ($CDCl_3$) δ 0.80-2.00 (17H,m), 2.68 (2H,m), 4.39 (1H,m), 4.63 (1H,m); 10b: nmr ($CDCl_3$) δ 1.60-2.20 (4H,m), 2.72 (2H,m), 2.87 (2H,m), 4.40 (1H,m), 4.70 (1H,m), 7.22 (5H,brs); 10c: nmr ($CDCl_3$) δ 0.92 (3H,t,J=7 Hz), 1.00-2.20 (10H,m), 2.68 (2H,m), 4.39 (1H,m), 4.68 (1H,m); 13: mp 91-93°C; nmr ($CDCl_3$) δ 2.13 (2H,dd,J=3.6, 7.5 Hz), 2.76 (2H,m), 4.16 (2H,d=5 Hz), 4.52 (1H,m), 5.06 (1H,m), 6.92 (3H,m), 7.25 (2H,m).

(Received in USA 12 July 1982)